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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,657	05/25/2000	Misako Mizuno	029430-454	6902

21839 7590 12/06/2002

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EXAMINER
KUBELIK, ANNE R.

ART UNIT	PAPER NUMBER
1638	26

DATE MAILED: 12/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/577,657	Applicant(s) MIZUNO ET AL.
	Examiner Anne R. Kubelik	Art Unit 1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13-17,20,21 and 23-28* is/are pending in the application.

4a) Of the above claim(s) *8-10,15 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 13-14, 16-17, 20-21, 23 and 27-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3 October, 2002, has been entered.

2. The cancellation of claim 22 and the amendment of claims 1-2, 4-5, 14, 17, 20-21 and 23 requested in Paper No. 25, filed 3 October, 2002, have been entered. Claims 1-10, 13-17 and 20-21 and 23-28 are pending. Claims 8-10, 15 and 24-26 remain withdrawn from consideration as being drawn to nonelected inventions. Claims 1-7, 13-14, 16-17, 20-21, 23 and 27-28 are examined.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The substitute specification allegedly filed 3 October, 2002, has not been entered because it was not sent. A substitute specification is still required for the reasons specified in the Office action mailed 16 October 2001.

Response to Amendment

5. The objection to claim 14 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is WITHDRAWN in light of amendments to the claim.

Claim Objections

6. Claims 1, 4, 7 and 20-21 are objected to because of the following informalities:

Claims 1 and 4 lack an article before "N-methyl" in line 3.

Claim 7 lacks an article before "N-methyl" in line 2.

In claim 16, a comma should be inserted before "wherein".

In claim 20, line 3, and claim 21, line 2"comprising" should be replaced with --, wherein the method comprises--.

7. Claim 23 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 20 is already drawn to a method of modifying whole plants, wherein the plant is a Coffea plant. If Applicant wishes to claim the method of claim 20, wherein a whole plant is cultured, claim 23 should be so amended.

Claim Rejections - 35 USC § 112

8. Claims 1-2, 4-5, 7, 13-14, 16-17, 20-21, 23 and 27-28 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:2 and plant cells and plants transformed with those nucleic acids, does not reasonably provide enablement for nucleic acids that encode SEQ ID NO:1, encode modified nucleic acids or that hybridize under unspecified stringency to nucleic acids that encode SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with

these claims. The rejection is modified from the reasons of record as set forth in the Office action mailed 3 May, 2002, as applied to claims 1-2, 4-5, 7, 13-14, 16-17, 20-23 and 27-28. Applicant's arguments filed 3 October, 2002, have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding SEQ ID NO:1 or a nucleic acid that hybridizes under "stringent conditions" to a nucleic acid that encodes SEQ ID NO:1 and that encode an enzyme that is an N3-methyl transferase, a theobromine N1 methyl transferase and a paraxanthine N3 methyl transferase, vectors comprising the nucleic acids, plant cells or plants comprising the vectors, a method of producing a plant secondary metabolite and a method of modifying the concentration of caffeine in a *Coffea* plant.

The instant specification, however, only provides guidance for isolation of N methyl transferase from *Camellia sinensis* var. *Yabukita* (example 1); amino acid sequencing of the N-terminal portion of the enzyme to produce SEQ ID NO:4 (example 2); use of a primer based on that sequence as a probe against a cDNA library from an unspecified source to isolate SEQ ID NO:5 (example 4); use of RT-PCR to isolate the coding sequence (SEQ ID NO:3, which encodes SEQ ID NO:1) from a tea cDNA library (examples 4-7); 5'-RACE to isolate the 5' upstream region to produce a gene sequence of SEQ ID NO:2 (example 8); expression of the enzyme in *E. coli* and testing of enzyme activities to show that the enzyme has the activities of an N3-methyl transferase, a theobromine N1 methyl transferase and a paraxanthine N3 methyl transferase (example 9); and antisense suppression of caffeine synthesis in coffee (example 10).

The instant specification fails to provide guidance for the isolation or construction of nucleic acids that hybridize under "stringent conditions" and that encode an enzyme that is an

N3-methyl transferase, a theobromine N1 methyl transferase and a paraxanthine N3 methyl transferase. The exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NOs:2-3 are not provided.

The specification fails to provide guidance for which amino acids are critical for protein function and which are not and can thus be altered. One method, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). The nucleic acids encoding all these mutated proteins, however, would hybridize under very high stringency to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities. Making all possible single amino acid substitutions in a 356 amino acid long protein like that encoded by SEQ ID NO:2 would require making and analyzing 19^{356} nucleic acids. Because nucleic acids that hybridize to nucleic acids

that encode SEQ ID NO:2 would have many more than a single substitution, nucleic acids with many more substitutions would need to be made and analyzed. As the specification does not provide guidance for this nucleic acid modification, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims, if such nucleic acids are even obtainable.

As discussed in the prior Office action, SEQ ID NO:1 does not appear to be the entire protein sequence. Kato et al (2000, Nature 406:956-957) teach a gene encoding a caffeine synthase that is identical to the caffeine synthase of the instant invention except the published enzyme is 13 amino acids longer at its N-terminal (see sequence search results sent with the Office action of 16 October 2001). All experiments involving transformation used a DNA comprising SEQ ID NO:2, which is almost identical to the nucleic acid taught by Kato et al and would encode the full-length enzyme. There is no evidence to suggest that a nucleic acid encoding only SEQ ID NO:1 would function to encode an enzyme with the listed properties, especially since the starting ATG is missing.

As the specification does not describe the isolation of any nucleic acid other than SEQ ID NOs:2-3 or the transformation of any plant with any nucleic acid other than SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith,, to identify those nucleic acids that encode proteins with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities, if such enzymes are even obtainable and those plants with altered concentrations of caffeine, xanthine, paraxanthine or theobromine, if such plants are even obtainable.

Applicant urges that it is well within the purview of the skilled artisan and the teachings of the specification to modify nucleotide sequences and determine if they encode a protein with the claimed activities, but amended the claim to indicate that the nucleic acid hybridizes under stringent conditions; this method if making these nucleic acids is disclosed on pg 5-8 of the specification (response pg 6-7). This is not found persuasive because pg 5-8 of the originally filed specification do not teach such methods. Pg 12-14 of the originally filed specification only provide general guidance for hybridization and PCR and do not teach hybridization and wash conditions or PCR conditions or primers that WILL isolate a nucleic acid encoding an enzyme with the three recited activities, other than SEQ ID NOs:2-3.

Applicant urges that unlike the situation in *Amgen*, the claims identify the scope within which the analogs fall and recite methods of producing those analogs. Applicant urges that the structural requirements for producing such compounds have been disclosed on pg 7-11 and 22-29 of the specification (response pg 7-8). This is not found persuasive because no wash conditions are recited in the hybridization methods. Additionally, pg 7-11 and 22-29 of the specification do not teach the structural features of any other N-methyl transferase than that encoded by SEQ ID NO:2 and does not teach the amino acid motifs critical for function.

Applicant urges that example 9 teaches that although SEQ ID NO:1 is not the entire protein sequence, it functions to encode an enzyme with the listed properties (response pg 9). This is not found persuasive because in example 9, *E. coli* was transformed with a nucleic acid of SEQ ID NO:2, which would encode a protein longer than SEQ ID NO:1. Applicant is invited to provide a Declaration showing data in which *E. coli* transformed with a nucleic acid that only encodes SEQ ID NO:1, with no starting ATG, produces an enzyme with the listed properties.

Applicant urges that the antisense suppression claims have been amended to limit the method to Coffea and limit the secondary plant metabolite in claim 21 to only caffeine (response pg 9-10). This is not found persuasive. The claims are also drawn to modifying the "composition" of caffeine (versus changing profile, ratio, or concentration). The instant specification provides no guidance for altering the "composition" of caffeine.

9. Claims 1-2, 4-5, 7, 13-14, 16-17, 20-21, 23 and 27-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 3 May, 2002, as applied to claims 1-2, 4-5, 7, 13-14, 16-17, 20-23 and 27-28. Applicant's arguments filed 3 October, 2002, have been fully considered but they are not persuasive.

Applicant urges that the specification on pg 7-11 recited structural features and stringent hybridization conditions and that it is within the purview of one of skill in the art to modify nucleic acids, given that the genetic code and enzyme assays are well-known (response pg 10).

This is not found persuasive. The specification does not describe the structural features, *i.e.*, the sequence, of nucleic acids that hybridize to a nucleic acid that encodes SEQ ID NO:1 and that encode a protein with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activites, other than SEQ ID NOs:2-3. The only sequences recited in the originally filed specification, on pg 7-11, are SEQ ID NOs:1-3, and on pg 11, nucleic acid encoding proteins with varying percent identities to SEQ ID NO:1. However, the

critical structural motifs that distinguish nucleic acids that encode functional enzymes from those that do not are not described.

10. Claims 1-7, 13-14, 16-17, 20-21, 23 and 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated in part for the reasons of record as set forth in the Office action mailed 3 May, 2002, as applied to claims 1-7, 13-14, 16-17, 20-23 and 27-28, and for the new reasons indicated below. Applicant's arguments filed 3 October, 2002, have been fully considered but they are not persuasive.

Applicant urges that the claims have been amended to over come these rejections (response pg 12-14). This is not found persuasive for the reasons indicated below.

Claims 1(b) and 4(b) lack antecedent basis for the limitation "said modified nucleic sequence".

Claims 1(b) and 4(b) are indefinite in their recitation of "stringent conditions". The specification does not define stringent conditions.

Claims 2 and 5 are indefinite in their recitation of "hybridized at a ... to overnight". Because the wash conditions are recited, nor are they unambiguously defined in the specification, the stringency of the conditions are unclear.

Claims 2 and 5 are indefinite in their recitation of "said nucleotide sequence (a) or said nucleotide sequence (b)". It is not clear is Applicant really wished to claim "The isolated DNA molecule as claimed in claim 1, wherein the stringent conditions are ...." or if Applicant was

trying to claim the nucleic acid more broadly than the parent claim. As currently claimed, the claim does not further limit the parent claim, as any nucleic acid can be hybridized under any hybridization conditions.

Claims 3 and 6 lack antecedent basis for the limitation "said nucleotide sequence (a)".

By position in claim 7 "in plant cells" appears to modify "DNA molecule". It is suggested that "a promoter ... cells" be replaced with --a plant promoter, wherein the vector expresses the N-methyl transferase in plant cells.--

Claim 20 lacks antecedent basis for the limitation "the transformed ... whole plant" in line 3.

Claim 21 is indefinite because it lacks agreement between the preamble of the methods and the positive method steps. Methods must be circular; the final step must generate the item the method is intended to produce. The method or modifying the concentration of caffeine in claim 21 ends in modifying "a" composition of caffeine, when it should end in the modification of the concentration of caffeine. It is also not clear what it means to modify "a" composition of caffeine.

11. Claims 1-7, 13-14, 16-17, 20-21, 23 and 27-28 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid encoding SEQ ID NO:1 or encoding a N-methyl transferase with 7-methylxanthine N3 methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
December 5, 2002

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